Introduction to SleepImage®
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### Contents

**Introduction** ................................................................................................. 4
- Understanding the SleepImage Benefits .......................................................... 4
- Understanding the SleepImage Science ............................................................ 6
- SleepImage Output Parameters ........................................................................ 10

**SleepImage in Sleep (Disorder) Management** ............................................. 14
- Expected Values - Sleep Quality and Sleep Pathology .................................... 14
- Sleep in Children .............................................................................................. 14
- Sleep in Adults .................................................................................................. 16

**Understanding the SleepImage Spectrogram** ............................................. 17
- Full View Spectrogram .................................................................................... 17
  - Stable Sleep or High Frequency Coupling - HFC ........................................ 17
  - Unstable Sleep or Low Frequency Coupling - LFC ...................................... 18
  - Wake & REM sleep or Very Low Frequency Coupling - vLFC .................... 18
- 3D View Spectrogram ...................................................................................... 18

**Reviewing SleepImage Graphics & Reports** ................................................ 19
- Review SleepImage Graphics for Associations & Patterns ............................ 21
- Patterns ............................................................................................................ 22

**Distinguishing Sleep Disordered Breathing Types** ..................................... 23
- 3D Spectrogram - Obstructive Sleep Apnea .................................................... 23
- 3D Spectrogram - Central Sleep Apnea .......................................................... 24
- 3D Spectrogram - Complex Sleep Apnea ......................................................... 24

**CPC Publications** ....................................................................................... 25
**Books** ............................................................................................................. 25
**Published Papers** .......................................................................................... 25
**References** .................................................................................................... 29
**Glossary** ........................................................................................................ 31
Introduction

The SleepImage® System is Food and Drug Administration (FDA) cleared Software as a medical Device (SaMD) that establishes Sleep Quality. The technology is based on Cardiopulmonary Coupling (CPC). The SleepImage algorithms analyze data, typically collected during sleep, derived from electrocardiogram (ECG) or photoplethysmogram (PPG) sensors to establish sleep opportunity, sleep quality, measure sleep duration and to detect sleep fragmentation, periodicity and cyclic variation of heart rate (CVHR). The SleepImage System, optionally analyzes SpO2 data to measure oxygen desaturation and to calculate the SleepImage Apnea Hypopnea Index (sAHI) that is FDA-cleared to aid clinical diagnosis of Sleep Disordered Breathing (SDB) in children and adults.

The SleepImage System is patented, cloud-based and Health Insurance Portability and Accountability Act (HIPAA) compliant and is intended for use by, or on the order of, a Healthcare Professional to aid in the evaluation of sleep disorders and for diagnosis and management of sleep disordered breathing in children and adults. When oxygen saturation data (SpO2) is collected simultaneously with the ECG- or PLETH-data (from a PPG sensor) for CPC analysis, the SleepImage software automatically calculates and displays the SleepImage Apnea Hypopnea Index (sAHI). The SleepImage System optionally graphs accelerometer data, that can display snoring and body position from actigraphy if these signal are recorded on the torso.

The SleepImage System is cleared for use in various countries around the world. This document is intended to be relevant for clinical users in all countries where the SleepImage System is cleared for use, is available in the English language only and is intended for general educational purpose. It is not intended to be Instructions for Use of the SleepImage System, for that please refer to SleepImage System Instructions for Use, available on www.sleepimage.com. For information on which countries the SleepImage System is available, please contact support@sleepimage.com.

Understanding the SleepImage Benefits

Good sleep quality is crucial for good health. One of the key benefits of using the SleepImage system in clinical practice is that, unlike most clinical sleep measurements, it is not restricted to measure sleep disordered breathing. SleepImage is a comprehensive measure of sleep health, presented through easy to understand biomarkers, that are presented with expected thresholds and color-coded results for each biomarker. The SleepImage FDA-clearance states that “SleepImage establishes Sleep Quality.” The Sleep Quality Index (SQI) is a summary biomarker of sleep health, cleared as a unit of measure, with a scale of 0 – 100, that has demonstrated a direct relationship with health outcomes in clinical studies.

SleepImage is a tool that can enhance clinical practice across all medical specialties, due to the fact that prior to the onset of any chronic disease, symptoms are present, and prior to symptoms there are reflections of changes in the autonomic nervous system (ANS) regulation that are not obvious. The SleepImage System is based on measuring biomarkers regulated by the ANS, heart rate variability (HRV) and respiration, during sleep when there are minimum environmental stimuli that can affect the ANS as happens during wake. The sleep period, on average, represents one third of a person’s life and getting sufficient good quality sleep at the right times is vital for good health and well-being as during sleep muscles and tissues are rebuild, memories are reorganize and consolidate for learning, and the immune system is strengthened. This can only happen when sleep is dominated by parasympathetic activity. The SleepImage output clearly distinguishes between parasympathetic and sympathetic dominance as ‘Stable’ and ‘Unstable’ sleep reflecting sleep health. That is why SleepImage brings value beyond the ability to diagnose sleep disordered breathing.
The SleepImage System Features and Benefits are summarized as follows:

<table>
<thead>
<tr>
<th>Patient Populations</th>
<th>SleepImage</th>
<th>PSG</th>
<th>HSAT</th>
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<tbody>
<tr>
<td>Asymptomatic</td>
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<tr>
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<td>✓</td>
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<td>Adults</td>
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</table>

<table>
<thead>
<tr>
<th>Types of Testing</th>
<th>Sleep Image</th>
<th>PSG</th>
<th>HSAT</th>
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<tr>
<td>Sleep Disorder Evaluation¹</td>
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<td></td>
<td></td>
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<tr>
<td>Sleep Disorder Screening</td>
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<td></td>
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<tr>
<td>OSA Diagnosis in Children</td>
<td>✓</td>
<td>✓</td>
<td></td>
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<tr>
<td>OSA Diagnosis in Adults</td>
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<tr>
<td>Treatment Tracking</td>
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<table>
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<tr>
<th>Test Output</th>
<th>Sleep Image</th>
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<tr>
<td>Phenotype OSA vs. CSA²</td>
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<td></td>
</tr>
</tbody>
</table>

¹ Clinical evaluation to determine symptoms of Insomnia or Sleep Apnea.
² OSA = Obstructive Sleep Apnea; CSA = Central / Complex Sleep Apnea

For the purpose of diagnosing sleep disordered breathing, the FDA-clearance for SleepImage states the following:

“Clinical evaluation has confirmed that the SleepImage System auto-scoring algorithms calculating the SleepImage Apnea Hypopnea Index (sAHI) generate comparable output to human manual scoring of an Apnea Hypopnea Index (AHI) from Polysomnography (PSG) studies, using American Academy of Sleep Medicine (AASM) scoring guidelines for children and adult patients.” [https://www.accessdata.fda.gov/cdrh_docs/pdf18/K182618.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf18/K182618.pdf)
Understanding the SleepImage Science

The SleepImage Cardiopulmonary Coupling (CPC) analysis is based on continuously and evenly sampled data from electrocardiogram (ECG) or photoplethysmogram (PPG) sensors to generate reports of sleep quality, sleep duration and sleep pathology to aid in the evaluation of sleep disorders, where it may inform or drive clinical management.

The SleepImage System provides clinical users with access to the raw data collected for manual interpretation of the study output. The data collected contains information on heart rate, heart (pulse) rate variability (HRV/PRV) as a measure of autonomic drive, as well as tidal volume fluctuations in respiration, called Electrocardiogram Derived Respiration (EDR) and Plethysmograph Derived Respiration (PDR), respectively, that is utilized for the CPC-analysis (Figure 1).

Cardiopulmonary Coupling analysis is based on patented algorithms developed and validated by sleep researchers, using continuous, evenly sampled, normal sinus rhythm ECG- or PLETH (plethysmogram from a PPG sensor)-signal as the only input requirement.

The validation of Cardiopulmonary Coupling (CPC) utilized clinical Polysomnography (PSG) as the standard upon which it was compared. Simultaneous SleepImage and PSG recordings were performed, on data that presenting periods of sleep identified by both systems that were compared for validation and published. Please refer to Publications Reference List which can be found on the last few pages of this document.

Both HRV/PRV and respiration are strongly modulated by autonomic sleep regulating mechanisms. The CPC-software utilizes mathematical and frequency analysis to calculate synchronization between HRV/PRV and respiration to provide visualization of sleep states and sleep pathologies. The Sleep Spectrogram demonstrates that there are clear boundaries between parasympathetic dominance (Stable sleep or High Frequency Coupling (HFC)) and sympathetic dominance (Unstable sleep or Low Frequency Coupling (LFC)). The spectrogram provides a clear view of sleep health during the entire sleep period, that is useful for sleep disorder evaluation and to track therapy efficacy. SleepImage is a helpful tool to monitor therapy efficacy as successful therapy for any diseases or conditions that affect sleep will demonstrate a relative increase in stable sleep and relative decrease in unstable sleep. (Figure 2)
The medical literature historically divided sleep into NREM-sleep and REM sleep, with NREM-sleep having four stages, that later were reduced to three stages (by eliminating Stage 4). Stage 3 represents “deep sleep” or “slow wave sleep” a stage where the brain almost exclusively produces slow delta waves. Stage 1 has brief periods and is usually a transition stage between wake and sleep. Stage 2 is defined as a state when cortical brain waves slow down and eye movements stop, but still with an occasional burst of faster brain waves. How the biologic role of NREM sleep is associated with delta power is unclear. Restricting such periods produces adverse consequences similar to those of total sleep deprivation including sleepiness and metabolic dysregulation. Delta power as a proportion of total EEG power is highest during the initial cycles of NREM sleep, and gradually decreases across the biological night and shows rebound effects after a period of sleep deprivation.

It is important to note that CPC does not rely on the same data input streams as PSG. Rather than the primary dependence of PSG on interpretation of EEG morphology, CPC utilizes the physiological changes that occur with sleep via the Autonomic Nervous System (ANS) through the “lower” brain centers and networks (including thalamus, hypothalamus, and hippocampus). It integrates information from brain electrical activity, respiration and autonomic drives, capturing the essence of sleep, making traditional “sleep staging” comparison a misnomer. The metrics are independent of absolute EEG amplitudes and thus are not constrained by the “loss” of slow wave sleep with age.
While PSG requires interpretation of observations (manual or automated) from EEG morphology to determine stages of NREM sleep, CPC displays autonomic nervous system regulation that has this distinct bi-modal structure demonstrating that sleep only has two distinct types, driven by sympathetic or parasympathetic dominance. This concept is supported by various biological system behavior like being either awake or asleep and when sleeping, being either in non-rapid eye movement (NREM) sleep or in rapid eye movement (REM) sleep.

Therefore, rather than the conventional graded classification of NREM stage 1, 2 and 3 that is based on interpretation of EEG morphology, CPC represents NREM sleep based on ANS morphology, and the software generated output is fully automated. CPC directly reports distinct alternating and abruptly varying periods of strong high and low frequency cardiopulmonary coupling as Stable sleep (High Frequency Coupling, HFC) and Unstable sleep (Low Frequency Coupling, LFC).

When comparing Stable NREM-sleep using CPC to traditional sleep staging from PSG, Stable NREM sleep is equivalent to part of Stage 2 and all of Stage 3 NREM sleep derived from PSG. Research has demonstrated the correlation between Stable sleep (HFC) and Delta Waves (deep sleep). In this state, desirable sleep features dominate, including high vagal tone/sinus arrhythmia, blood pressure dipping, high slow wave power, and stable breathing. Unstable sleep (LFC) equates to the part of NREM sleep that is unstable, meaning all of Stage 1 and part of Stage 2 NREM sleep. In this stage, generally less desirable features dominate, such as cyclic variation in heart rate, absence of blood pressure dipping, tidal volume fluctuations (with sleep apnea of a degree exceeding clinical thresholds) and lower delta power. REM sleep and Wake are detected and separated through spectral power analysis of CPC (Very Low Frequency Coupling; vLFC). During REM-sleep the person is near motionless or in state of “skeletal muscular paralysis” where the primary mechanical motion is the eyes. The physiology of REM sleep and Wake is closely linked from the standpoint of PSG with the electrooculography (EOG) as the main tool for distinguishing between the two states. CPC defines REM sleep into Stable and Unstable REM sleep based on frequency analysis of how the dominant CPC state has been classified as vLFC, where fragmented REM sleep is often accompanied by elevated Low Frequency Coupling.

![Graph showing the relationship between HFC and normalized delta power.](image)

Figure 3. The figure above reveals the relationship between HFC and normalized delta power (blue line) during simultaneous data collection using CPC and PSG as discussed in the paper “Relationship between delta power and the electrocardiogram-derived CPC Spectrogram: possible implications for assessing the effectiveness of sleep”. Dr. Robert Joseph Thomas et al. Sleep Med. 2014 Jan; 15(1); 125-131.
During the validation of the CPC technology, output comparison to tens of thousands of PSG studies were performed and a high level of correlation with PSG sleep power mapping has been confirmed. The ebb and flow of slow wave power is the accepted marker of sleep drive in humans and in non-human species. Delta power measured from surface EEG correlates with ECG- or PLETH-derived Cardiopulmonary Coupling high-frequency power, further supporting a link between cortical EEG electrical activity and brainstem-related cardiorespiratory functions.²,³

This correlation between EEG delta power and high-frequency Cardiopulmonary Coupling is consistent with strong “top-down” modulation of autonomic and cardiorespiratory activity. The Sleep-Spectrogram in Figure 3 demonstrates the correlation comparing Stable sleep (HFC) and normalized delta power (blue line) during simultaneous data collection using CPC- and PSG-analysis.

While CPC and PSG analyze and present biological activity during sleep from different directions (Heart Rate Variability coupled with Respiration vs. Cortical Brain Wave regulation, respectively), they both reflect sleep. Sleep regulation is complex, but sleep is mainly regulated by two parallel mechanisms, homeostatic regulation and circadian regulation, controlled by the suprachiasmatic nucleus (SCN), thalamic structures and adenosine accumulation, respectively. The two methods (CPC and PSG) do therefore not vary as much as it may seem at first, as demonstrated in Figure 4.

Both CPC and PSG are quite capable instruments to assess sleep, with some important differences. The CPC Sleep Spectrogram and the software generated biomarkers of sleep quality, sleep pathology as well as sleep duration and latency, provide a new and practical approach to assess sleep as a vital sign of health. The SleepImage method is particularly useful to track sleep health over time to identify relative changes in sleep quality, and in individuals with sleep disorders, for disease management, whether it is for insomnia or Sleep Disordered Breathing. The simple interface offers the potential to treat sleep disorders as other chronic diseases, by repeated testing in patients’ natural sleep environment over multiple nights and multiple time points to optimize disease management.¹¹-¹³
Further description and information on the technology of Cardiopulmonary Coupling is described in a medical textbook on sleep medicine, Principles and Practice of Sleep Medicine, (Kryger – Roth – Dement) Sixth Edition, Chapter 166. Cardiopulmonary Coupling Sleep Spectrogram. ²

**SleepImage Output Parameters**

**Stable sleep** (High-frequency coupling; 0.1-0.4Hz) is a biomarker of stable NREM sleep, which is characterized by stable breathing, high vagal tone, a non-cyclic alternating pattern (n-CAP) on the electroencephalogram (EEG), high relative delta power, blood pressure dipping, and stable arousal threshold. This state may be considered as “effective” NREM sleep. Effective sleep enables the normal functions of sleep, across multiple dimensions (e.g. neuronal network health, metabolic etc.), such that spending periods in this state enables recovery and restoration processes.²³

**Unstable sleep** (Low-frequency coupling; 0.01-0.1Hz) is a biomarker of unstable NREM, with exactly opposite features when compared to stable sleep: low-frequency tidal volume fluctuations, cyclic variation in heart rate, a cyclic alternating pattern (CAP), electroencephalogram (EEG) low relative delta power, non-dipping of blood pressure and variable arousal thresholds. This state may be considered “ineffective” NREM sleep. Ineffective sleep fails to accomplish the normal functions of healthy sleep. A subset of low-frequency coupling is termed Elevated Low-Frequency Coupling (e-LFC) and has two subsets; an indicator of Periodicity (elevated low frequency narrow band; e-LFCₙ₈) and Fragmentation (elevated low frequency coupling broad band (e-LFC₅₈)).

Sleep-fragmenting stimuli increases unstable sleep (low-frequency coupling), and sleep-consolidating stimuli increases stable sleep (high-frequency coupling) as a percentage of sleep, thereby allowing dynamic tracking of sleep physiology and pathology in health and disease²³¹⁴

**Fragmentation** (elevated low frequency coupling narrow-band e-LFCₙ₈) is a subset of low-frequency coupling during NREM sleep which is an indicator of sleep pathology (e.g. pain) or airway disordered breathing patterns like Obstructive Sleep Apnea (OSA) and Upper Airway Resistance Syndrome (UARS).²¹⁴, ₁⁵⁻₁⁷

**Periodicity** (elevated low frequency coupling narrow-band e-LFCₙ₈) is a subset of low-frequency coupling, consisting of periodic-type breathing patterns that may occur during NREM and/or REM and indicates sustained periods of Central Sleep Apnea (CSA) and periodic breathing, or “physiologic” periodicity due to Periodic Leg Movements (PLM’s) or speech during sleep.⁷¹⁴,₁⁶

**Sleep Quality Index (SQI)** is a summary index of the CPC biomarkers of sleep quality, sleep stability, sleep fragmentation and periodicity, and provides a meaningful unit of measure of sleep health. The SQI is displayed on a scale of 0-100 and with expected values for both children and adults. The SQI can be used as a “unit of measure” for sleep and is useful to track sleep health over time, whether to identify the need for further clinical investigation or to track therapy. The SQI is easily communicated and relatable for the patient or other lay persons, while at the same time being a comprehensive measure of sleep health based on clinical validation.⁵,¹³,¹⁵⁻¹⁸

**Sleep Apnea Indicator (SAI)** provides a measure of SDB and is based on detecting oscillations in cardiac intervals associated with prolonged cycles of sleep apnea, based on Cyclic Variation of Heart Rate (CVHR) during unstable breathing (tidal volume fluctuations in breathing). During each apnea event, blood oxygen decreases and is accompanied by a physiological reaction of bradycardia and, when breathing resumes, a relative tachycardia and thus hypoxemia is reflected in the CPC-output. When SAI is presented with the Sleep Quality Index, Fragmentation and Periodicity, it is possible to use the SAI to not only help detect apneas, but also to differentiate between obstructive and central/complex sleep apnea.¹⁵⁻¹⁹

The SAI is displayed from signals recorded with either an ECG- or PPG-sensor, and is therefore always reported with CPC output, irrespective of whether SpO₂ is recorded or not. The SAI is presented as a percentage of the sleep period where cyclic variation of heart rate (CVHR) is detected during unstable sleep. CVHR can be detected during stable sleep and then often may reflect events that are typically scored as mild hypopneas but may also be triggered by other pathologies such as Periodic Limb Movements (PLMS) or Restless Leg Syndrome (RLS). For clinical evaluation it is
important to consider both SAI that is likely to reflect apnea events that disturb sleep to lower the SQI, and CVHR that is likely to reflect milder apneas and hypopneas that may or may not disturb sleep to lower the SQI.

The SAI can be compared numerically to the AHI from PSG-studies, although it is based on different physiological signals and the unit of measure to quantify sleep apnea is different. SAI can be perceived as a severity biomarker for CPC-derived parameters of SDB, while the AHI is literally a prevalence measure counting events per hour of sleep. Despite that, classification of SDB utilizing CPC-analysis is based on the same premises as AHI, the common biomarker used to quantify severity of SDB, as Mild, Moderate and Severe based on the American Academy of Sleep Medicine (AASM) guidelines. Table 1 summarizes a comparison of SAI- and CVHR-values to AHI from Polysomnography (PSG) studies at each of the severity threshold levels for mild, moderate and severe sleep apnea in children and adults. Both SAI and CVHR are useful metrics to inform and guide clinical management of sleep disorders and when used with SQI values tracked over time and have clinical utility to guide timing of SDB interventions, to guide therapy and tracking disease management in both children and adults.

| Table 1. Results of comparing automated SleepImage Apnea Indicator (SAI/CVHR) and manually scored AHI (PSG) output. |
|---|---|---|---|
| SAI/CVHR vs AHI | Mild | Moderate | Severe |
| Adults | SAI | 79% | 79% | 87% |
| | CVHR | 83% | 81% | 89% |
| Children | SAI | 88% | 87% | 96% |
| | CVHR | 88% | 85% | 94% |

Sleep Apnea is associated with significantly increased risk of cardiovascular morbidity and mortality and cardiac autonomic dysfunction presented as decreased heart rate variability (HRV) and predominant cardiovascular sympathetic activity that persists during wakefulness. Cardiac autonomic dysfunction ultimately leads to a fixed heart rate due to progressive dysfunction of the cardiac sympathetic nervous system. HRV is considered the earliest and most frequent indicator of symptomatic cardiovascular autonomic dysfunction. The Sleep Apnea Indicator is an ineffective tool to detect apneas in this subgroup of sleep apnea patients, as they do not exhibit the oscillatory heart rate dynamics, but the CPC e-LFC biomarkers and the sAHI are useful to aid in the diagnosis of Sleep Disordered Breathing in this patient population. In patients with Atrial Fibrillation, complex patterns cannot be identified and the chaos of the autonomic nervous system results in less meaningful CPC output and thus CPC testing in atrial fibrillation is not advised.

Apnea Hypopnea Index (sAHI) is an automated measure of Apnea/Hypopnea events, comparable to the American Academy of Sleep Medicine (AASM) scoring guidelines of the Apnea Hypopnea Index (AHI) for both adults and children. When oxygen data (SpO2) is available the SleepImage System analyzes the SpO2-data to generate desaturation events, display an SpO2 graph and automatically calculate SleepImage Apnea Hypopnea Index (sAHI) by combining CPC-analysis and hypoxic events that are detected through the SpO2-signal where a qualifying event is characterized by a minimum of ten (10) seconds in duration and a 3%-oxygen desaturation. The sAHI is FDA-cleared to aid diagnosis of Sleep Disordered Breathing (SDB) in both children and adults and follows AASM categorization (mild, moderate, severe) as summarized in table 2.

| Table 2: Categorization of Sleep Apnea by American Academy of Sleep Medicine (AASM) for adults and children (events/hr) |
|---|---|---|---|---|
| | No Sleep Apnea | Mild Sleep Apnea | Moderate Sleep Apnea | Severe Sleep Apnea |
| Adults | AHI/REI < 5.0 | AHI/REI ≥5.0 to < 15.0 | AHI/REI ≥15.0 to < 30.0 | AHI/REI ≥30.0 |
| Children | AHI < 1.0 | AHI ≥1.0 to < 5.0 | AHI ≥5.0 to < 10.0 | AHI ≥10.0 |
The sAHI, like the Apnea Hypopnea Index (AHI), reports the number of paused breathing events during the sleep period. Events are displayed based on CPC sleep states (Stable and Unstable NREM sleep, REM sleep and the two sub-categories of unstable NREM sleep; Fragmentation (elevated low-frequency coupling broad band, eLFCBB) and Periodicity (elevated low-frequency coupling narrow band, eLFCNB). Additionally, events are presented with and without CVHR to aid in clinical interpretations and management of SDB. When reviewing the overall sAHI score, it is recommended to consider SDB events concurrent with CPC sleep states to evaluate and determine disease severity and for differential diagnosis of Obstructive (OSA), Central (CSA) or Complex/Mixed Sleep Apnea, using the pathology biomarkers of Fragmentation (associated with obstruction) and Periodicity (associated with periodic breathing).7,14,15,19

Safety and Effectiveness of SleepImage Apnea Index (sAHI) and performance, was validated by comparing the fully automated software generated sAHI by comparison to manually derived AHI from in-laboratory PSG-studies currently considered as the “reference standard” collected in prospective clinical trials including both children and adults. Additionally, from prospective clinical trials in adults were data collected with Home Sleep Apnea Tests (HSAT), sAHI was compared to Respiratory Event Index (REI). All comparisons are based on definition of disease severity categorization of Sleep Apnea based on definition by the American Academy of Sleep Medicine (AASM), table 2.

The comparison of sAHI to AHI is based on published guidelines from the American Academy of Sleep Medicine (AASM), “Obstructive Sleep Apnea Devices for Out-Of-Center (OOC) Testing: Technology Evaluation”21 This guidance was prepared to “help clinicians decide which out-of-center (OOC) testing devices are appropriate for diagnosing obstructive sleep apnea (OSA) and is based on emphasizing Sensitivity and Positive Likelihood Ratio. Additionally, guidelines from the American Academy of Pediatrics (AAP),22 calling for information to be available for physicians to familiarize themselves with sensitivities, specificities and predictive values when outcome of a test is compared to polysomnography to evaluate the test for use in clinical diagnosis are included and as tonsillectomy is the primary intervention for pediatric obstructive sleep apnea (POSA), and clinical guidelines from the American Academy of Otolaryngology – Head and Neck Surgery Foundation have been incorporated (Table 3).23

In children, AHI from a total of 1,334 PSG-studies were compared to the software generated sAHI. In the cohort 39% of the children had no disease (n=518), 45% had mild sleep apnea (n=601), 9% moderate sleep apnea (n=123) and 7% had severe sleep apnea (n=92).

In adults, a total of 839 studies were analyzed from PSG (n=189) and from HSAT (n=572) where 12% had no sleep apnea (n=102), 30% had mild sleep apnea (n=251), 37% moderate sleep apnea (n=313) and 21% severe sleep apnea (n=173).

The performance-testing, comparing the two indexes sAHI (CPC-output) and AHI (PSG-output), did demonstrate strong correlation as well as significant agreement in both defining events/hour and to identify SDB categories (no-disease, mild sleep apnea, moderate sleep apnea, severe sleep apnea) in both adult and in children. The results are summarized in table 3 and based on AASM recommendations Likelihood Ratios are included as well as, Predictive Values by recommendation from AAP. The difference between Likelihood Ratios and Predictive Values, can be explained as follows:

Likelihood Ratios (LR) are used to assess the value of performing a diagnostic test and is performed to determine whether a test result usefully changes the probability that a disease state exists. AASM guideline defines acceptable results as sensitivity of at least 82.5% and LR+ of at least 5 at an in-lab AHI of at least 5, demonstrating a 95% post-test probability of the disease based on 80% pre-test probability of the disease.21

Predictive Values (PV) reflect the diagnostic power of the test and depend on sensitivity, specificity and disease prevalence, as well as the reporting probability of the patient being positive/negative based on a positive/negative test result. AAP does not have a guideline for what values are sufficient to generate passing results to diagnose a disease.22
Table 3. Results of comparing automated sAHI (CPC) and manually scored AHI (PSG) output.

<table>
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<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td>sAHI vs AHI</td>
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<tr>
<td><strong>Agreement</strong></td>
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<td></td>
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<tr>
<td>Adults</td>
<td>96.3%</td>
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<td>Children</td>
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<td>98.1%</td>
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<td>[.941, .964]</td>
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<td>Adults</td>
<td>98.7%</td>
<td>92.6%</td>
<td>95.1%</td>
</tr>
<tr>
<td>CI95%</td>
<td>[.970, 1.000]</td>
<td>[.869, .983]</td>
<td>[.835, .994]</td>
</tr>
<tr>
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<td>89.3%</td>
<td>91.3%</td>
</tr>
<tr>
<td>CI95%</td>
<td>[.887, .927]</td>
<td>[.852, .934]</td>
<td>[.855, .971]</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>84.8%</td>
<td>88.9%</td>
<td>100%</td>
</tr>
<tr>
<td>CI95%</td>
<td>[.726, .971]</td>
<td>[.830, .948]</td>
<td>[.975, 1.000]</td>
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<tr>
<td>Children</td>
<td>86.7%</td>
<td>96.3%</td>
<td>98.6%</td>
</tr>
<tr>
<td>CI95%</td>
<td>[.834, .895]</td>
<td>[.951, .974]</td>
<td>[.978, .992]</td>
</tr>
<tr>
<td><strong>Positive Likelihood Ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>6.52</td>
<td>8.33</td>
<td>28001</td>
</tr>
<tr>
<td>Children</td>
<td>6.81</td>
<td>24.37</td>
<td>66.71</td>
</tr>
<tr>
<td><strong>Negative Likelihood Ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>0.015</td>
<td>0.083</td>
<td>0.060</td>
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<tr>
<td>Children</td>
<td>0.107</td>
<td>0.111</td>
<td>0.088</td>
</tr>
<tr>
<td><strong>Positive Predictive Values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>96.9%</td>
<td>86.2%</td>
<td>100%</td>
</tr>
<tr>
<td>Children</td>
<td>91.5%</td>
<td>82.4%</td>
<td>83.2%</td>
</tr>
<tr>
<td><strong>Negative Predictive Values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>93.3%</td>
<td>94.1%</td>
<td>98.7%</td>
</tr>
<tr>
<td>Children</td>
<td>85.5%</td>
<td>97.9%</td>
<td>99.4%</td>
</tr>
</tbody>
</table>

Neither academic association requires an overall agreement to be reported, although, in practical terms, is what is most commonly used to determine test accuracy and is therefore reported as well in Table 3.

Both SAI and sAHI are meaningful indices to evaluate sleep apnea in children and adults. The SAI, based on CVHR events during unstable sleep, has a scale of 0 – 100. The sAHI is an event counter of paused breathing events per hour of sleep, the same as AHI derived from in-laboratory PSG-studies.

The SleepImage Apnea Hypopnea Index (sAHI) is intended to aid healthcare professionals in diagnosis and management of Sleep Disordered Breathing (SDB) in children, adolescents and adults. When the test output is used to aid diagnosis or management of SDB in children, consideration should be given to clinical guidelines that (1) require the clinician to determine if the test result is inconclusive for diagnosis before determining the need for another test, assessing the risk of an adverse treatment outcome because of inappropriate management; and (2) recognize the role for individualized decisions based on needs of the child and its caregiver(s). A definitive diagnosis of SDB requires both clinical and objective sleep data. Because of age related airway growth, children in particular stand to benefit from evaluation over a time period. Diagnosis of SDB in children is defined as AHI > 1/per hour of sleep. However, the AHI must be considered in the context of the child’s health, symptoms, and daytime functional impairment to most accurately assess SDB significance, severity, and impact. The fact that majority of treatment-related changes in outcomes of SDB in children are not causally attributable to polysomnographic resolution or changes in severity may underscore a limited utility of polysomnographic thresholds in the management of childhood SDB, calling for additional biomarkers in the disease management process.

The benefit of using the SleepImage System with an AHI output is that it provides both an event count (AHI) to help quantify Sleep Disordered Breathing (SDB), while also categorizing paused breathing events in context of the SleepImage Spectrogram. It presents an overview of the sleep period, the SleepImage biomarkers that measure sleep stability, sleep quality, as well as Fragmentation and Periodicity, including the ability to differentiate between obstructive (e-LFCes) and central/complex sleep apnea (e-LFCne).
While sleep disordered breathing patterns are commonly quantified using AHI, the SleepImage biomarkers are still useful for identification and management of SDB when oxygen saturation is not recorded. Using SQI and SAI together with Fragmentation (e-LFCBB) and Periodicity (e-LFCNB) it is possible to identify the presence of sleep disordered breathing and categorize between obstructive, central and complex sleep apnea. In certain countries, an sAHI is required to qualify for treatment of SDB. When this is the case, SleepImage recommends that a diagnosis of SDB is confirmed with a SleepImage test that records oxygen saturation to generate a report that includes sAHI, which is FDA-cleared to aid diagnosis of sleep apnea in children and adults.

SleepImage in Sleep (Disorder) Management

The SleepImage method, being simple and cost effective, offers the opportunity to track changes in sleep over time, as part of both sleep health and in sleep disorder management.

Night-to-night variability in sleep is recognized and this variance should be expected to increase between nights with increased sleep disorders (sleep pathology) or the presence of comorbidity. It is well documented in peer-reviewed clinical publications how sleep apnea severity can vary considerably from night to night as has been reported in SDB-patients undergoing PSG-studies on consecutive nights or one month apart, where changes in AHI were observed to be in the range of 18%-65%. When sleep disorders are suspected, it is important to treat them as other chronic conditions that can present different levels of symptoms over time, with multiple testing. Measuring sleep in patients’ normal sleep environment by acquiring data over multiple nights and on multiple time points to capture sleep physiology and pathology in order to mitigate the night-to-night variability, respects the chronic nature of sleep disorders and should improve the diagnostic process prior to initiating therapy, disease management and patient outcomes.

None of the values for the SleepImage biomarkers should be considered absolute threshold values; they are expected to be generally similar when using the same sensor type, but accounting for the night to night variability previously discussed is important. Some differences should be expected over time and between different sensors (ECG vs PPG), due to either environmental conditions or signal specific conditions that can affect the recording. For clinical use, it is recommended to consistently use the same sensor type in the patient’s natural sleep environment as much as possible. Repeated studies over time are always recommended for any clinical decision-making for sleep disorders.

Expected Values - Sleep Quality and Sleep Pathology

<table>
<thead>
<tr>
<th>Expected Values</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Quality Index (SQI)</td>
<td>&gt;55</td>
<td>&gt;70</td>
</tr>
<tr>
<td>Sleep Apnea Indicator (SAI) Mild / Moderate / Severe threshold markers</td>
<td>≥5 / ≥15 / ≥30</td>
<td>≥1 / ≥5 / ≥10</td>
</tr>
<tr>
<td>Apnea Hypopnea Index (sAHI) Mild / Moderate / Severe threshold markers</td>
<td>≥5 / ≥15 / ≥30</td>
<td>≥1 / ≥5 / ≥10</td>
</tr>
<tr>
<td>Elevated Low Frequency Coupling, Broad Band (e-LFCBB)</td>
<td>&lt;15</td>
<td>&lt;8</td>
</tr>
<tr>
<td>Elevated Low Frequency Coupling, Narrow Band (e-LFCNB)</td>
<td>≤2</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4. Expected values for CPC biomarkers are not absolute thresholds and need to be considered in context of patients’ sleep complaints, comorbidity and patient history.

Sleep in Children

Clinical guidelines regarding diagnosis of sleep disordered breathing (SDB) in children, emphasize that attempts to specify severity of SDB and make treatment decisions solely on the basis of the Respiratory Effort Index (REI) or Apnea Hypopnea Index (AHI) and minimum oxygen saturation may lead to misclassification.
The most common form obstructive sleep disordered breathing (oSDB), characterized by an abnormal respiratory and ventilation patterns during sleep, is a highly prevalent condition in children with disease severity ranging from primary habitual snoring (6-25%) to obstructive sleep apnea (OSA), diagnosed when apnea-hypopnea index (AHI) $\geq 1.0$ on nocturnal polysomnography (PSG).

Tonsillar-hypertrophy and obesity are the most common risk factors for OSA in children and tonsillectomy is recommended as first-in-line therapy for children with tonsillar-hypertrophy and OSA.29

The considerable variability in symptom presentation in children makes OSA difficult to diagnose, demanding increased awareness of SDB in children among clinicians. Excessive daytime sleepiness is not a frequently reported symptom in children, and sleep fragmentation and disrupted sleep architecture often presents as hyperactivity, difficulties concentrating, attention- behavioral- and mood-problems, enuresis, persistent mouth breathing with dry mouth and morning headaches.28, 30,31

To further complicate disease management of OSA in children, spontaneous polysomnographic improvements are well known and documented (46%) as well as residual disease following surgery with less than a third of children with OSA achieving complete resolution with surgery.34,35 Additionally, surgery may potentially cause both serious short-term surgical complications and in the long-term significantly increased delayed respiratory, allergic and infectious sequelae.36-39

Although several screening questionnaires have been developed to identify children with OSA, they have not proven accurate, caregiver reports of symptoms correlate poorly with PSG findings, and subjective clinical evaluation of tonsillar-size is not a reliable indicator of need for surgery or surgical success.40-43

Both the American Academy of Pediatrics (AAP) and the American Academy of Sleep Medicine (AASM) recommend a PSG-study to objectively assess and diagnose OSA prior to surgery, as questionnaires alone do not provide a good diagnostic prediction of OSA in children. These academic guidelines to establish objective evidence of OSA prior to surgical decisions are frequently bypassed though.44 This may be caused by limited access to pediatric sleep laboratories, high cost of testing with increased parent out-of-pocket expenses, or reported inconvenience for both the child and their caregivers.23,39

The fact that majority of treatment-related changes in outcomes of OSA in children are not causally attributable to polysomnographic resolution or changes in severity calls for additional sleep metrics that can be tracked over time.36 The SleepImage System is FDA-cleared for diagnosis of OSA in children based AHI, additionally the system displays sleep biomarkers of sleep duration, sleep quality, Fragmentation and Periodicity. SleepImage offers a simple, low cost tool to track dynamics of SDB in children, which may be a more appropriate method than making a therapy decision from presentation of symptoms at one specific point in time. The SleepImage test is not intrusive for the child, offering the potential to measure multiple nights of sleep, to guide clinical decisions in children suspected of suffering from OSA, based on clinically validated biomarkers to capture dynamics of the disease. The SleepImage biomarkers include:15-18

1. Sleep quality (captured by the Sleep Quality Index – SQI)
2. Cyclic variation of heart rate (captured by Sleep Apnea Indicator – SAI)
3. Fragmentation, indicative of arousals (captured by elevated low frequency coupling broad-band – eLFCbb)
4. Periodicity, indicative of periodic breathing/central sleep apnea (captured by elevated low frequency coupling narrow-band e-LFCnb)
5. Time spent below an oxygen saturation of 90% and 88%
6. State of sleep (REM vs. NREM stable/unstable)
7. Sleep opportunity, sleep latency, and sleep duration.

The symptom variability of OSA in children as well as the complexity of the disease, mandates a careful data-driven clinical decision-making process prior to therapy, including surgery, as well as implementation of therapy-tracking post intervention for objective evaluation with longitudinal care to improve clinical management. If left untreated the disease may adversely affect the child’s neurocognitive, behavioral, cardiovascular and cardiometabolic health over time.18,31,33
Sleep in Adults

The same approach for sleep management in adults is important as PSG and HSAT generally do not offer the opportunity for repeated testing prior to disease diagnosis or to track efficacy of therapy. Currently the ratio of undiagnosed SDB is estimated to be around 85% of the patient population and according to a recent publication in the Lancet by Benjafield et al. more than 936 million people are estimated to have the disease. Long-term compliance on therapy is considered generally low and is problematic as effectiveness of therapy is greatly dependent on consistent use. The lack of compliance to therapy may be caused by patients’ own subjective evaluation of not finding the benefit from therapy to outweigh the burden of the therapy or be caused by negative effects of CPAP-therapy on sleep quality (SQI). Sleep quality evaluation at baseline as well as repeated testing for therapy efficacy is therefore highly desirable for both patients and their clinicians to improve clinical management of sleep disorders.4,13,46,47

Only with this kind of objective testing, will the opportunity for more comprehensive phenotypic profiling in both clinical management of sleep disorders as well as in design and conduction of research studies be fully utilized. Sleep disorder management needs to become comparable to how other chronic conditions like diabetes or hypertension are managed.4,13 A change in clinical protocols to this extent could have a meaningful and measurable positive impact on patient outcomes and on quality of research to provide insight into sleep in both health and disease. Improvements in management of sleep disorders will only be achievable with access to accurate and actionable clinical sleep-tests that are evidence based, simple, low-cost and scalable, and can be self-administered in the patients’ own natural sleep environment.

The SleepImage system offers a fully automated and rigorously validated output, that is simple to use both for patients and clinicians for unique insight into sleep health and sleep regulation:

1) Stable sleep tracks slow wave power and results of repeated testing could provide new insights into night-to-night sleep homeostatic mechanism.2,3,12

2) Substantial overlap in symptom presentation of insomnia and OSA is documented. This advances a need for a new perspective for methods capturing both insomnia and OSA before making diagnostic decisions and initiation of therapy. Offering access to objective, medically validated tests for patients with sleep complaints who currently are considered ineligible for PSG or HSAT testing, could fill a void in clinical management of sleep disorders.12,17,48

3) sAHI detects and categorizes sleep apnea. The CPC_ biomarkers of Periodicity (e-LFCan) and Fragmentation (e-LFCCa) further make it simple to distinguish between Obstructive, Central and Complex/Mixed Sleep Apnea. The method offers improvements in disease evaluation and tracking of therapy efficacy, including detection of persistence or emergence of loop gain features, all from recording of a simple signal and automated analysis. In general, periodic breathing and hypocapnic central apnea are NREM-dominant and do not occur in REM-sleep (exception, a patient with congestive heart failure who can demonstrate periodic breathing during wake) and are features of idiopathic central sleep apnea, opiate-induced sleep apnea and high-altitude periodic breathing. In patients with complex sleep apnea treated with continuous positive airway pressure, therapy can induce or amplify respiratory instability and the loop gain has found to be higher in patients in whom central apneas persist on therapy than in patients with short cycle periodic breathing or treatment-emergent central sleep apnea.7,14,15,49-51

4) SAI documents autonomic reaction to altered breathing and oxygen desaturations and has a good correlation with AH1.15-18 The SAI (CVHR) should be used in context of other SleepImage biomarkers and as a parameter to track over time.

5) The possibility to record sleep for more than one night in the patient’s natural sleep environment should offer opportunity for improved clinical management of sleep disorders. Change in clinical protocols to objectively test all patients with sleep complaints for more than one night before any therapy is initiated (insomnia, sleep apnea etc.) could have a meaningful and measurable positive impact on both disease management and public health.
Understanding the SleepImage Spectrogram

The SleepImage System graphically displays the coupling of heart rate variability (HRV) or pulse rate variability (PRV) and respiration activity (electrocardiogram derived respiration, EDR or plethysmograph derived respiration, PDR) in the Sleep Spectrogram. On the front-view Spectrogram, time (hh:mm) is displayed on the horizontal axis, and frequency (Hz) is on the vertical axis. When both data streams (HRV - EDR or PRV - PDR) are in-phase (coupled), peaks are generated on the graph to form a visual representation of the frequencies collected during the recording.

Full View Spectrogram

The full view Spectrogram displays the peaks and oscillation pattern of HFC, LFC and vLFC for the time series. The vertical axis uses frequency range 0.004Hz to 0.5Hz and time in hours on the horizontal axis.

HFC peak amplitude is in relation to the amount of coupling or synchronization between the curves generated by the heart rate variability (HRV) and respiratory rate activity. Greater coupling results in higher amplitude peaks. Low amplitude peaks result from less overlap between the curves generated by heart rate variability and respiratory rate activity. A lack of coupling between these two input data streams (HRV and respiratory rate activity) will result in zero value and no peak generation.

Stable Sleep or High Frequency Coupling - HFC

Stable sleep (High frequency coupling) is displayed on the Spectrogram as dark blue peaks in the frequency range of 0.1 - 0.5Hz. Most Stable sleep occurs during part of NREM-stage-2 and NREM-stage-3, especially with the EEG morphology called noncyclic alternating pattern (n-CAP) and delta waves. Stable sleep is a biomarker of integrated stable
NREM sleep and is associated with periods of stable breathing, high vagal tone, generally a non-cyclic alternating pattern on the electroencephalogram, high relative delta power, physiologic blood pressure dipping, and stable arousal threshold.

Unstable Sleep or Low Frequency Coupling - LFC

Unstable (Low frequency coupling) is displayed on the Spectrogram as light blue peaks in the frequency range of 0.01 - 0.1Hz a. Unstable sleep is a biomarker of integrated unstable NREM sleep, with opposite features to Stable sleep and occurs during NREM-stage-1 and part of NREM-stage-2 sleep. Unstable sleep is associated with EEG activities called cyclic alternating pattern (CAP), periods of fluctuating breathing patterns (tidal volume fluctuations), cyclic variations in heart rate (CVHR), blood pressure non-dipping and variable arousal thresholds. Fragmented REM sleep has low-frequency coupling characteristics.

Wake & REM sleep or Very Low Frequency Coupling - vLFC

Very low frequency coupling (vLFC) is displayed on the Spectrogram as orange peaks in the frequency range of 0.004 - 0.01Hz and represent REM sleep or wake.

During the course of a night’s sleep, spontaneous shifts occur between stable and unstable sleep. Oscillations between stable and unstable sleep are expected to modulate in 30-90 minute-cycles ranging from 4-8 cycles for an adult’s 8-hour healthy sleep and correspond to the alternating periods of NREM and REM sleep (Figure 5). Disease states negatively impact this pattern. Healthy, stable sleep, dominated by high vagal tone, results in characteristic heart rate variability, where the heart rate slows down and speeds up in synchrony with regular respiration. This is normal rhythm and is associated with stable NREM sleep (HFC).

3D View Spectrogram

The SleepImage Spectrogram can be displayed in an interactive three-dimensional view by rotating the image for a more detailed observation of the low frequency range. Using the 3D view helps to interpret and differentiate between Sleep-Disordered Breathing (SDB) phenotypes (Obstructive vs. Non-Obstructive).

3D View Spectrogram: The SleepImage Spectrogram can be displayed in an interactive three-dimensional view by rotating the image for a more detailed observation of the low frequency range. Using the 3D view helps to interpret and differentiate between Sleep-Disordered Breathing (SDB) phenotypes (Obstructive vs. Non-Obstructive).
1. **Check Signal Quality.** Only predominantly green signal quality should be considered for clinical decision-making. Yellow and Red signal should be evaluated for artifacts as opposed to arrhythmias.

2. **Evaluate Sleep Quality.** The SQI indicates unhealthy sleep as SQI <55 (adults) or <70 (children). SQI is a summary of sleep stability, fragmentation and periodicity on a scale from 0 – 100. Sleep Efficiency is the ratio of Total Sleep Time divided by Sleep Opportunity and should be >85%.

3. **Evaluate Sleep Opportunity** which is defined by time in bed allocated to sleep, including Sleep Latency and Sleep Duration. Sleep Duration includes Total Sleep Time (TST) and Wake After Sleep Onset (WASO). Expected Sleep Latency is generally defined as <30 min. Sleep Duration but is defined by age groups. Although Insomnia cannot be diagnosed from a single night of sleep, Sleep Latency and Sleep Efficiency are the most commonly used metrics to evaluate symptoms of Insomnia. Low SQI without SDB may additionally indicate insomnia.

4. **Evaluate Sleep Apnea.** The SleepImage Apnea Hypopnea Index (sAHI) (when SpO₂ is recorded) and/or Sleep Apnea Indicator (SAI) indicate the presence of sleep apnea. The sAHI is cleared to aid diagnosis of Sleep Disordered Breathing and is categorized as ‘Mild’; ‘Moderate’ and ‘Severe’ with values for Children for each category ≥1, ≥5 and ≥10 respectively and for Adults values for each category are ≥5, ≥15 and ≥30 respectively. SAI can indicate SDB with good agreement against sAHI values despite being a different method to detect and quantify sleep apnea and has the same threshold values as sAHI for children and adults.
5. **Review Sleep Pathology.** The Sleep Pathology biomarkers are Fragmentation (e-LFCBB) indicates sleep fragmentation, arousals and obstructive apneas, and Periodicity (e-LFCNB) indicating central apneas.

6. **Review Sleep Stability.** Stable Sleep is the most important indicator of restorative sleep that with good agreement with Slow Wave (Delta) Sleep in PSG recordings and is expected to be >50% in adults and >65% in children.

7. **Review Transitions, Snore and Body Position.** Sleep Stability is affected by transitions to Wake that should be evaluated to enhance clinical investigation. Snore and Body Position (when recorded) may indicate Positional Sleep Apnea, as snore is generally most prevalent when sleeping on the back (Supine).

8. **Review CVHR.** CVHR during Stable Sleep is excluded from calculations of the Sleep Apnea Indicator (SAI), but it may indicate events typically scored as mild hypopnea events in PSG studies and can be caused by leg movements. Review CVHR during REM sleep to differentiate REM sleep apnea.

9. **Review Oxygen Summary and Apnea Events (when recorded).** The percentage of oxygen summary events <90% are an indicator of the severity of hypoxic events during sleep. The Apnea Count table provides a summary of apnea events in relation to sleep stability and concurrent CVHR events that may help clinical evaluation of apnea severity beyond the prevalence that is reported by the sAHI. It is further helpful to investigate apnea events with view to the relationship between the SQI and sAHI (SAI) to evaluate how severely sleep apnea is affecting sleep quality.

10. **Summary,** the SleepImage Report automatically summarizes the key metrics from CPC analysis to aid the Clinician in summarizing the Clinical Evaluation and recommendations for further testing, further evaluation (referral of patient to another clinician) or therapy.
1. **Spectrogram:** Review for HFC (stable sleep), LFC (unstable sleep) and vLFC (wake and REM sleep) distribution during the recording period in association with body position, movement, snoring (when recorded), CVHR (cyclic variation of heart rate, presented as SAI (Sleep Apnea Indicator) and sAHI is (when recorded) on the report.

2. **Hypnogram:** Observe the frequency of transitions between Stable Sleep, Unstable Sleep, REM Sleep and Wake. A high number of transitions indicate more fragmented sleep. Healthy sleep is indicated by higher prevalence of Stable Sleep during the first third of the sleep period, with increased REM sleep towards the last third of the sleep period.

3. **Sleep Disordered Breathing:** Look for presence of fragmentation and periodicity. Fragmentation indicates events that may be caused by obstructive apnea or pain and are termed e-LFCBB. Periodicity indicates metronomic activity that may be caused by central apnea or periodic breathing and are termed e-LFCNB.

4. **CVHR:** Evaluate CVHR in association with the Spectrogram, body position, snoring, movement and oxygen saturation. CVHR is a marker of changes in heart rate happening during and at the cessation of an apnea event.

5. **Snore and Body Position:** Evaluate snore (when recorded) in association with sleep stability, body position (when recorded), CVHR and oxygen saturation (when recorded). Snore in Supine position may indicate Positional Sleep Apnea. and examine the snore trace for a crescendo pattern indicating upper airway resistance (the report displays snore count and duration).

6. **Desaturation and SpO₂ (when recorded):** Review desaturation events and correlate in association with stable, unstable and REM sleep, look for concurrent CVHR and correlation with body position and snoring (when recorded). Areas of SpO₂ signal loss are often demonstrated by a large and sudden drop in SpO₂.

7. **Actigraphy (when recorded):** Associate level of Actigraphy with concurrent events, assess any patterns across the recording period and examine the actigraphy graph - see next page.

8. **Signal Quality:** Evaluate the quality of the signal during the recording period. Red indicates signal loss and therefore the CPC algorithm is not able to produce accurate data during these periods. If long periods of signal loss are present it is recommended to repeat the sleep recording.

9. **Adjust the study period (Clinician Users):** Drag the green and red markers on the green line at the bottom of the spectrogram to the desired beginning and end of the study and click the Recalculate button.

10. **Toggle HFC, LFC and vLFC peaks (Clinician Users):** of the spectrogram on and off to isolate coupling types by clicking the labeled HFC, LFC and vLFC markers to hide/display the peaks by type.
Patterns

After analyzing Associations, an overview of Patterns within the Traces below the Spectrogram in your SleepImage account should be considered. By reviewing the Spectrogram from Left (Start) to Right (End) and examining the Traces that coincide with the timeline of the recording, you can observe concurrent events.

1. **Actigraphy Trace (when recorded):** Increased actigraphy associated with periods of unstable sleep

2. **Snore Trace (when recorded):** Snoring with crescendo pattern during periods of unstable sleep

3. **SpO₂ Trace:** Oxygen saturation of areas <90% during periods of e-LFC_{bb} (with and without CVHR) and e-LFC_{nb} (with and without CVHR).
Distinguishing Sleep Disordered Breathing Types

Sleep Disordered Breathing (SDB) comprises a wide spectrum of sleep-related breathing abnormalities. There are three major categories of SDB:

1. **Obstructive Sleep Apnea (OSA)** is the most common one and is related to increased upper airway resistance and includes snoring, upper airway resistance syndrome (UARS) and obstructive sleep apnea (OSA). Patients who suffer from OSA periodically struggle to breathe and are unable to inhale effectively because the airway has collapsed.

2. **Central Sleep Apnea (CSA)** happens when the brain temporarily stops sending signals to the muscles that control breathing. This condition often occurs in people who have certain medical problems and when not associated with another disease it is called idiopathic central sleep apnea. A condition, Cheyne-Stokes respiration, subtype of CSA presents similarly on the CPC-Spectrogram.

3. **Complex/Mixed Sleep Apnea** is most often seen in patients who have been diagnosed with OSA and treated with positive airway pressure but fail to breathe normally after the airway has been opened and their sleep apnea assumes the characteristics of central sleep apnea.

An exceptional feature of the SleepImage CPC analysis is its capacity to easily distinguish between SDB types. Each SDB type has a visually discernable Spectrogram pattern that makes identification simple and intuitive. The CPC algorithms identify Obstructive Sleep Apnea pathology as fragmentation, presented as increased elevated LFC ‘broad band’ (e-LFCBB). Periodic-type breathing pattern (i.e. Central Sleep Apnea) is identified by elevated LFC ‘narrow band’ (e-LFCNB). Complex/Mixed Sleep Apnea, a combination with both Obstructive and Central components in an alternating pattern of elevated LFC broad and narrow bands.

To aid the clinician in identifying individuals with SDB when oxygen saturation is not recorded, the SleepImage system offers the Sleep Apnea Indicator (SAI) that is automatically calculated from known changes in heart rate that occur during apneas, called Cyclic Variation of Heart Rate (CVHR). A simple way to explain CVHR is that it consists of bradycardia during apnea followed by a relative tachycardia when breathing resumes. Although SAI is a different measure with a different unit of measure when compared to sAHI, it is possible to use the same numeric values in both metrics to evaluate the presence of sleep apnea. For Mild, Moderate and Severe Sleep Apnea in adults the values are ≥5 / ≥15 / ≥30 and in children the values are ≥1 / ≥5 / ≥10 respectively.

3D Spectrogram - Obstructive Sleep Apnea

Figure 8. The 3D View Spectrogram - Obstructive Sleep Apnea shows a “broad” distribution of the peaks called Elevated Low Frequency Coupling broad-band (e-LFCBB). 
3D Spectrogram - Central Sleep Apnea

Central Sleep Apnea or periodic breathing is represented by narrow red colored peaks as e-LFC_{NB} on the 3D Spectrogram view and identifies patterns of breathing or movement having a “narrow band” LFC profile.

![Figure 9. 3D Spectrogram - Central Sleep Apnea](image)

The system colors these peaks red to make it easier for users to identify the periodicity.

3D Spectrogram - Complex Sleep Apnea

A combination of both obstructive and central components showing narrow band e-LFC (e-LFC_{NB}) and broad band e-LFC (e-LFC_{BB}).

![Figure 10. 3D Spectrogram - Complex Sleep Apnea](image)

Figure 10. 3D Spectrogram - Complex Sleep Apnea is a combination of both obstructive and central components.
CPC Publications

Books


Published Papers

Technique


2. Y Ma, S Sun A new approach to sleep study: does heart tell us a lot? Sleep Med 2013; e188-e189. DOI: 10.1016/j.sleep.2013.11.446


Relationship between CPC and PSG


Therapy

1. Hilmisson H, Magnusdottir S. Beyond the Apnea Hypopnea Index (AHI): Importance of Sleep Quality in Management of Obstructive Sleep Apnea and Related Morbidity and Mortality in Patients with Cardiovascular Disease. World Sleep Congress 2019 [Sleep Medicine December 2019].


Pediatric


Sleep Disordered Breathing


5. Al Ashry HS, Thomas RJ, Hilmisson H. A Combination Index of Low Frequency Cardio-Pulmonary -Coupling and Oxygen Desaturation has a Strong Correlation with the Apnea Hypopnea Index. Sleep 2019; 42(Suppl_1). A188. DOI: 10.1093/sleep/zss067.466


Insomnia/Mental Health


Other


17. Chien PL, SU HF, Hsieh PC et al. Sleep Quality among Female Hospital Staff Nurses. Sleep Disord 2013; Article ID 283490 DOI: 10.1155/2013/283490


References


4. Hilimsson H, Magnusdottir S. Beyond the Apnea Hypopnea Index (AHI): The Importance of Sleep Quality in Addition to AHI in Management of Sleep Disordered Breathing and Related Mortality in Patients with Cardiovascular Disease. [Data introduced at the World Sleep Congress in Vancouver in September 2019].


12. Thornton, A, Maijer R, Ewert C. Multidisciplinary Care for Obstructive Sleep Apnea in the Age of “Personalized” Sleep Medicine. [ Data introduced at the World Sleep Congress in Vancouver in September 2019]


20. Al Ashry HS, Thomas RJ, Hilimsson H. A Combination Index of Low Frequency Cardio-Pulmonary-Coupling and Oxygen Desaturation has a Strong Correlation with the Apnea Hypopnea Index. Sleep 2019. 42(Suppl_1). A188. DOI: 10.1093/sleep/zzs067.466.


40. Cote CJ, Posner KL, Domino KB. Death or neurologic injury after tonsillectomy in children with a focus on obstructive sleep apnea: Houston, we have a problem! Anesth Analg 2014; 118 (6): 1276-1283. DOI: 10.1213/ANE.0b013e3182389f07.


42. Coté CJ, Posner KL, Domino KB. Death or neurologic injury after tonsillectomy in children with a focus on obstructive sleep apnea: Houston, we have a problem! Anesth Analg 2014; 118 (6): 1276-1283. DOI: 10.1213/ANE.0b013e3182389f07.


Glossary

AASM: American Academy of Sleep Medicine
CAP: Cyclic Alternating Pattern
CPAP: Continuous Positive Airway Pressure
CPC: Cardiopulmonary Coupling - the synchronization of heart rate variability and breathing activity
CSA: Central Sleep Apnea
CVHR: Cyclic Variation of Heart Rate. Refers to characteristic heart rate pattern that happens during and at cessation of apnea events.
DSAT: Desaturation Events
e-LFCbb: Elevated Low Frequency Coupling, Broad Band - an indicator of sleep fragmentation (e.g. pain) or airway disordered breathing patterns (e.g. Obstructive Sleep Apnea, Upper Airway Resistance. (see Understanding the CPC Spectrogram)
e-LFCnb: Elevated Low Frequency Coupling, Narrow Band - an indicator of periodic-type breathing patterns e.g. Central Sleep Apnea (see Understanding the CPC Spectrogram)
ECG (EKG): Electrocardiogram - recording the electrical activity of the heart over a period of time
EDR: Electrocardiogram Derived Respiration
EEG: Electroencephalogram - recording electrical activity of the brain along the scalp
HFC: High Frequency Coupling – an indicator of stable sleep (see Understanding the CPC Spectrogram)
HRV: Heart Rate Variability
LFC: Low Frequency Coupling – an indicator of unstable sleep (see Understanding the CPC Spectrogram)
N-CAP: Non-Cyclic Alternating Pattern
NREM: Non-Rapid Eye Movement
OSA: Obstructive Sleep Apnea
PDR: Plethysmograph Derived Respiration
PRV: Pulse Rate Variability
PSG: Polysomnography – an in-laboratory sleep study where each 30 sec window (epoch) is manually scored.
REM: Rapid Eye Movement
SA: Sleep Apnea
SAI: Sleep Apnea Indicator. Displays “one number” for apnea events through the recording period by automatically detecting known changes that occur in the cardiovascular system during periods of sleep disordered breathing.
sAHI: SleepImage Apnea Hypopnea Index
SaMD: Software as a Medical Device
SDB: Sleep Disordered Breathing - refers to a wide range of sleep-related breathing abnormalities
SpO2: Oxygen Saturation
SQI: Sleep Quality Index. Presents “one number” encompassing overall sleep health based on CPC metrics.
Spectrogram: Visual representation of the spectrum of the frequencies of Cardiopulmonary Coupling.
UARS: Upper Airway Resistance Syndrome
vLFC: Very Low Frequency Coupling – Wake/REM Sleep (see more in Understanding the CPC Spectrogram